REMARKS

Along with a Continued Prosecution Application Request, submitted herewith is an Information Disclosure Statement and Form PTO-1449 and copies of the references listed therein, along with payment of the required fee pursuant to 37 C.F.R. § 1.97(c).

Original claims 1-10 have been cancelled, and replaced with new claims 11-40 directed to methods of synthesizing various compounds, the compounds themselves, pharmaceutical compositions and methods of treatment.

The specification has been amended to recite the relationship with the parent case, namely that the present application claims priority to the provisional applications nos. 60/071,070 filed January 9, 1998 and 60/111,531 filed December 9, 1999, and that the present application is the U.S. national phase of PCT/US99/00419, filed January 8, 1999.

I. Objection to the specification

The specification is objected to as allegedly having several typographical and structural errors. Specifically, the formula of the phosphoramidite in the figure on the bottom of page 7, $(R_1O)_2PN^2_2$, has been cited as missing an "R" group from the formula, and on page 8, the spelling of 'diavalent' has been cited as being potentially incorrect. The specification was further objected to for failing to clearly describe the salts that are illustrated in the scheme on the bottom of page 8. Both of the typographical errors in the specification have been amended. Applicant submits that these errors were unintentional and obviously typographical in nature, and consequently no new matter has been added in making these corrections.

Applicant notes that the Examiner has objected to the specification for allegedly failing to describe the salts illustrated in the scheme on the bottom of page 8. However, it is well established that the specification and claims must be taken as a whole. One of skill in the art, in reading the present specification, would understand that the generic classification of "salt" does not refer only to compounds of ionic bonded character, but to those of covalent bonded character as well, and the numerous aspects of the drug-salt form, e.g. whether they are cations, anions, etc., the feasibility of salt formation for the pertinent compound, and the like [see, for example, "Handbook of Pharmaceutical Salts: Properties, Selection, and Use"; Stahl, P.H., and Wermuth, C.G., eds., Wiley-VCH, 2002; Chapters 4, 6-8 and 11]. Consequently, it is respectfully requested that this objection be withdrawn.

II. Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-10 were rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite in claiming the subject matter of the invention.

Applicant has cancelled claims 1-10 and added new claims 11-30, in order to more clearly point out and distinctly claim the subject matter that the Applicant regards as the invention. Applicant respectfully submits that the rejections of claims 1-10 under 35 U.S.C. § 112, ¶ 2 are now moot in light of their cancellation, and the rejection should be withdrawn.

III. Rejection under 35 U.S.C. § 102

Claim 9 was rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the patents to Rathbone, *et al.* (WO92/16486; hereinafter "Rathbone") and Pettit (U.S. Patent No. 5,561,122; hereinafter "the '122 patent"), and the journal article by Pettit, *et al.* (Anti-Cancer Drug Design 1995; hereinafter "the Pettit paper"). Specifically, the Examiner states that Rathbone discloses the compound of the combretastatin A-4 phosphate potassium salt, and the '122 patent and the Pettit paper both disclose the compound of the combretastatin A-4 phosphate potassium or sodium salt. This rejection has been carefully considered, and it is respectfully requested that it be withdrawn in view of the following.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference. *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677, 7 U.S.P.Q.2d 1315, 1317 (Fed. Cir. 1988). Furthermore, inherent anticipation requires that the missing descriptive material is necessarily present, not merely probably or possibly present in the prior art. *In re Robertson*, 169 F.3d 743, 49 USPQ.2d 1949 (Fed. Cir. 1999).

Rathbone suggests a convergent synthesis for the synthesis of combretastatin A-4, as well as specific phosphate salts and other derivatives for the purpose of enhancing the aqueous solubility characteristics of the parent compound (combretastatin A-4). According to the specification, the process is "characterised in that it is a convergent process that includes the step of reacting, in a Wittig coupling reaction, an ylide triphenyl phosphonium salt of a trialkoxyl

benzyl halide with a benzaldehyde compound:" (page 2, lines 21-24). The analogues of combretastatin A-4 which are generated are phosphate derivatives and salts thereof, as well as amino-acid carbamate derivatives, carbohydrate derivatives, and polyhydroxylated derivatives. Specifically described is the synthesis and analysis of the combretastatin A-4 phosphate diammonium salt (compound **7**, Example 2b, page 12, line 31 through page 13, line 30), and the combretastatin A-4 phosphate potassium salt (compound **8**, Example 2c, page 13, line 31 through page 14, line 19), among other derivatives of combretastatin A-4. According to the experimental procedure (pages 11-12), combretastatin A-4 was reacted with di-t-butyl N,N-diethylphosphoramidite in THF with tetrazole and mCPBA to generate the bis-t-butyl ester derivative (compound **6**). The ester was cleaved with trifluoroacetic acid in dichloromethane, and the appropriate salt was formed by the addition of concentrated ammonia solution (page 13, lines 6-7) or by treating the ammonium salt with Dowex 50 8X cation exchange resin, K^+ form (page 13, lines 35-37). Alternatively, the combretastatin A-4 phosphate potassium salt (**8**) can be formed as described in Example 4 (page 16, line 11 through page 19, line 32), wherein the phosphate ester (**6**) is formed *via* a Wittig reaction between 3,4,5-trimethoxybenzyl triphenylphosphonium bromide and 4-methoxy-3-(O-phosphate)benzaldehyde t-butyl ester (**12**). No mention or suggestion of other approaches, or other salts which can be synthesized, is made.

The '122 patent proposes water-soluble combretastatin A-4 phosphate prodrugs, specifically the ammonium (**1f**), di-potassium (**1g**) and di-sodium (**1h**) phosphate derivatives, for the purpose of increasing the water-solubility behavior of the parent compound, combretastatin A-4 (**1a**). The process described in the '122 patent includes reacting combretastatin A-4 with

bis(2,2,2-trichloroethyl)phosphorodichloridate ("Troc-Cl") in pyridine to generate the Troc phosphate (**1e**). The Troc-group is then removed using zinc dust in acetic acid to generate the phosphoric acid, followed by the use of an ion-exchange column (NH_4^+ form, K^+ form, or Na^+ form) to yield the ammonium hydrogen, dipotassium, or disodium combretastatin A-4 3'-O-phosphate, respectively (col. 2, lines 11-67). The '122 patent claims only the di-sodium combretastatin A-4 phosphate prodrug, and a method of treating cancer with this specific compound.

The Pettit paper describes a method of preparing phosphate prodrugs of combretastatin A-4 in order to overcome the very limited water solubility of the 3'-phenolic group which has purportedly complicated drug formulation of combretastatin A-4. As specifically described therein, the 3' phenol of combretastatin A-4 (**1a**) is reacted with bis(2,2,2-trichloroethyl)phosphorodichloridate in pyridine in order to form a bis(2,2,2-trichloroethyl) protected phosphate ester. The protecting group is then removed using a Zn-Cu couple in acetic acid with 2,4-pentanedione to complex zinc salts, generating the free phosphoric acid derivative. The phosphoric acid, without isolation, is then converted into a variety of derivatives including the ammonium (**1l**), potassium (**1m**), or sodium (**1n**) salt by passing the phosphoric acid derivative of combretastatin A-4 through the appropriate Dowex® 50 cation exchange column (NH_4^+, K^+ or Na^+ form), or alternatively sodium methoxide in the case of the disodium salt.

Applicant's present invention is directed to alternative methods to those described in the above references for the synthesis and generation of disodium combretastatin A-4 3'-O-phosphate and *trans*-combretastatin A-4 3'-O-phosphate disodium salt, as well as a variety of

other potentially useful phosphate compounds and/or salts, using previously undisclosed processes that allow for both rapid and large-scale production of the claimed compounds. As described in the specification, as well as in the claims as amended, the phosphate esters of the present invention can be formed by either one of two methods. In the first method, combretastatin A-4 phosphates can be produced by contacting combretastatin A-4, or the *trans*-isomer thereof, with a di(arylmethane)phosphite, a tetrahalomethane, a tertiary amine, and an acylation catalyst to form the protected phosphate ester (**3a**). In the second method, combretastatin A-4 or its trans- isomer is contacted with a phosphoramidite in a solvent with tetrazole and an oxidizing agent to form a phosphate ester (**3b-3c**). The phosphate esters (**3a-c**) can then be converted to the phosphate acid in one step using readily available reagents with minimal to no side-product formation, followed by conversion to the phosphate salts/compounds **5a-s** by treatment with the appropriate alkoxide, hydroxide, amine, or amine salt.

Rathbone does not disclose or suggest a method of producing combretastatin A-4 3'-phosphate, the *trans*-isomer thereof, or a variety of alternative salts thereof by contacting a stilbene such as combretastatin A-4 or its *trans*-isomer with a di(arylmethane)phosphite, a tetrahalomethane, a tertiary amine, and an acylation catalyst to form a phosphate ester, which is then converted to the phosphate prodrug by treatment with a trialkylhalo silane and the appropriate salt, alkoxide, hydroxide, amine or amine salt. Similarly, Rathbone does not disclose a method of producing disodium combretastatin A-4 3'-phosphate, the *trans*-isomer thereof, or a variety of alternative salts thereof by contacting a stilbene such as combretastatin A-4, or its *trans*-isomer, with a phosphoramidite, an oxidizing agent, and tetrazole to form a

phosphate ester, followed by contacting the phosphate ester with an acidic compound or a trialkylhalo silane to generate a phosphoric acid which can be converted to a prodrug by treatment with the appropriate alkoxide, hydroxide, amine, or amine salt. Rathbone proposes only methods of making the ammonium and potassium phosphate prodrugs of combretastatin A-4, using a convergent process which includes a Wittig reaction and using cation exchange resin to generate the ammonium and potassium phosphate salts. Rathbone makes no mention of forming salts other than the ammonium or potassium salts, and does not describe the formation of prodrugs of the *trans*-isomer of combretastatin A-4. Applicant's independent claims 11, 22, and 29 describe methods of producing phosphate prodrugs of both combretastatin A-4 and its *trans*-isomer comprising the step of contacting a stilbenes in a solvent with either a) di(arylmethyl)phosphite in the presence of tetrahalomethane and a tertiary amine, or b) a phosphoramidite, tetrazole, and an oxidizing agent where the phospharamidite is an aryl, arylmethyl, or alkyl phosphoramidite to produce a phosphate ester. Additionally, Applicant's present invention does not describe the preparation of potassium of ammonium phosphate salts of combretastatin A-4 or its *trans*-isomer. Because these elements of the Applicant's claimed invention are not shown or described in Rathbone or the Rathbone claims, this reference does not anticipate claims 11-40 of the present application under 35 U.S.C. § 102(b).

Similarly, both the '122 patent and the Pettit reference offer only methods of making the disodium combretastatin A-4 3'-O-phosphate, by using bis(2,2,2-trichloroethyl)phosphorochloridate to form 3'-O-bis(2,2,2-trichloroethyl)phsophoryl combretastatin A-4. Neither the '122 patent, nor the Pettit paper, disclose contacting

combretastatin A-4, or the *trans*-isomer thereof, with a phosphite or phosphoramidite to form a new phosphate ester of combretastatin A-4, which can then be mildly deprotected to generate the phosphate acid, a limitation appearing in new independent claims 11, 22, 29, and their dependent claims. As this element of Applicant's claimed invention is not shown or described by either the '122 patent or the Pettit paper, these references do not anticipate new claims 11-40 under 35 U.S.C. § 102(b).

In view of the foregoing, Applicant respectfully requests that the rejections under 35 U.S.C. § 102(b) be withdrawn.

Conclusion

In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding objections and rejections are respectfully requested. All amendments are made in a good faith effort to advance the prosecution on the merits. Applicant respectfully submits that no amendments have been made to the pending claims for the purpose of overcoming any prior art rejections that would restrict the literal scope of the claims or equivalents thereof. Applicant reserves the right to subsequently take up prosecution of the claims originally filed in this application in continuation, continuation-in-part, and/or divisional applications.

In view of the foregoing, Applicant respectfully requests early allowance of the claims.

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Respectfully submitted,

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I hereby certify that this paper and any documents referred to herein are being deposited on the date indicated above with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10, postage prepaid and addressed to Mail Stop CPA, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Louis A. Lofredo, Legal Assistant

6/5/03
Date of Signature